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THE DIAGNOSIS OF MALARIA FROM THE STANDPOINT OF THE PRACTITIONER IN ENGLAND.

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Fothergillian Medallist, 1902.

SLIPSHOD diagnosis is not to be commended. We must confess, however, that, so far as the interests of patients are concerned, in the vast majority of diseases, provided the physician abstain from a too active interference with natural processes, it matters little whether diagnosis be exact or even correct. In too many diseases we possess little or no power for good. Fortunately for the reputation of our art there are a few diseases over which we can exercise absolute or relative control; and just because we possess in the case of these remediable diseases this power, it is of the utmost importance that we recognise them, that we diagnose them accurately. The disease about the diagnosis of which I propose to offer a few remarks this evening—malaria—is one of these. For it, in quinine, we possess an almost infallible remedy. Hence, if we fail to recognise malaria when it is present, and in consequence of such failure in diagnosis omit to administer the appropriate remedy, the patient suffers, and we grossly fail in duty. Contrariwise, if in some given case we erroneously diagnose malaria and treat the patient accordingly, we certainly treat the case wrongly, perhaps miss the chance of cure by more appropriate means, waste a valuable drug, and certainly run the risk of damaging our own reputation. The ability to diagnose malaria is, therefore, a matter of high practical importance.

In those countries in which malaria is endemic and common, it not infrequently happens that the infection is overlooked. As a rule, however, it is the other way about; malaria is far too frequently assumed to be present where it has nothing whatever to do with the case. This remark is equally, if not more, applicable to certain cases of disease which come to England from abroad. Such is the exaggerated idea of the insalubrity of tropical countries, of the universal prevalence of malaria in them, that a very large

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proportion of the febrile, and even non-febrile, diseases coming from them to this country are diagnosed and treated as malarial. It happens far too often, both in England and in the tropics, that the practitioner, when in difficulties about a tropical patient, assumes the case to be malarial. The patients, likewise, are very prone to be content with and to endorse such a diagnosis, for they too, from one cause or another, have come to believe that in the matter of disease "tropics" spells "malaria." Somehow to many there seems to be a sort of fascination and appropriateness about the word "malaria," as if it carried with it mystery, romance, and explanation, such as is said to belong to the blessed word "Mesopotamia." In the course of 12 years' experience of London practice I have seen some two or three cases only in which malarial infection had been overlooked; in the same time I have seen a very large number of cases in which malaria had been diagnosed, but in which malaria was neither present nor had anything whatever to do with the symptoms.

The latter type of case I meet with so frequently that I thought, when asked to read a paper before this Society, I could not do better than choose for my subject this very practical matter of the diagnosis of malaria as we find it when imported into England.

Whatever may have been the difficulties in the way of reliable diagnosis of the infection in the past, recent discovery has enabled us to be precise and absolutely sure about it, at all events in 99 cases out of a 100. There are few diseases so easily diagnosed; nevertheless, and although nearly every member of the profession knows, in an academic sort of way, the principles on which the points of diagnosis are founded, my experience tells me that these principles are not applied systematically, nor in actual practice assessed at their proper value. Possibly it may serve some useful purpose if, availing myself of this opportunity, I recapitulate and accentuate these principles.

The pathognomonic indications of malarial infection may be conveniently arranged under these headings:—(1) The clinical; (2) the therapeutic; (3) the microscopical.

(1) *The Clinical Diagnosis.*—There are many signs and symptoms of malarial infection—fever, anæmia, icteric tinting of skin and scleræ, enlargement of the spleen and liver, gastro-intestinal disturbance, a tendency to spontaneous recovery and to subsequent recurrence. All or any of these may lead one to suspect, but not

one of them, nor the concurrence of all of them, justifies a positive diagnosis of malaria. None of them, and no grouping of them, is pathognomonic. They are present separately or variously combined in many other morbid conditions. They may justify in any given case a suspicion, but not a diagnosis, of malaria.

There is only one clinical symptom that justifies a positive diagnosis: this is periodicity, periodicity of a particular type—tertian or quartan periodicity—a rhythmical recurrence of symptoms every 48 or 72 hours. In no other morbid condition are these to be found, and wherever well marked malaria is present.

In malarial disease the appearance of quotidian periodicity is common enough; but it is only the appearance. It is very doubtful if true quotidian periodicity ever occurs in malaria; if it does it is certainly very rare. The parasites of malaria are either tertian or quartan in habit, and many of the symptoms they give rise to are correspondingly tertian or quartan in their recurrences. Multiple infection by two kinds of parasites, or by two or three generations of the same species of parasite, may give rise to double tertian or treble quartan infection with diurnal recurrence of symptoms; but this pathologically, whatever it may be clinically, is not a true quotidian periodicity. It is common enough in malaria, but I would insist it is not pathognomonic of malaria, for a similar quotidian periodicity is very general—in fact, is usual—in almost all febrile complaints. Therefore, to make quotidian periodicity a ground for a diagnosis of malaria is wrong. More than that, it is most dangerous, and is, perhaps, the commonest cause of erroneous diagnosis of malaria. Experience has made me formulate a rule for myself which I commend to you—have absolute confidence in tertian and quartan periodicity as a basis for a diagnosis of malarial infection, but distrust, or rather absolutely disregard, quotidian periodicity.

In tropical practice I have seen more mistakes from relying on quotidian periodicity as a ground for diagnosing malaria than from any other cause. The temptation to attach weight to it is often very strong, but I would again urge on you to harden your hearts against it.

When a patient from the tropics comes to you with a story of evening rigor, rise of temperature to 103° or perhaps 104°, and a profuse sweat, the idea of malaria naturally presents itself. Most probably the patient tells you he has malaria. And if one

finds the patient anæmic, and that his spleen is large, perhaps very large, the diagnosis of malaria seems to be clenched. But people abroad get splenic and spleno-medullary leucocythæmia, and other diseases in which the spleen is enlarged, as well as people in England, and such patients often have marked quotidian fever. These leucocythæmic and other kinds of enlarged spleen cases I frequently see on the supposition that they are malarial. Had the patients never been abroad, probably the idea of malaria would never have been entertained.

Another type of case in which there is enlargement of the spleen associated with anæmia and quotidian fever I occasionally see, probably because it, too, is sometimes supposed to be malarial. In a sense the cases I refer to are malarial, or, rather, post-malarial. I allude to what is known in Assam—where the condition in certain districts is very common and very fatal—as Kala-azar. The same condition occurs in other malarious countries, however. The patient gives a history of malarial attacks, which at first were controlled to some extent by quinine. After a time the recurring attacks became more frequent and less amenable to quinine. Finally, the fever resisted treatment, became quotidian, the spleen becoming permanently enlarged, the anæmia intense, the skin sallow or even melasmic, and, ultimately, in spite of treatment, the patient, if not cut off by some intercurrent disease, dies of pure anæmia. This disease, although possibly induced by malaria, has long ceased to be malaria—is, in fact, a post-malarial cachexia, brought about by organic changes in the blood organs, and induced possibly by some additional and distinct infection attacking organs already damaged by antecedent malaria.

I find that the presence of enlarged spleen is a bait that few resist when attempting the diagnosis of a quotidian fever in a patient from the tropics. The combination is so suggestive. But we must bear in mind that many people in the more malarious districts in the tropics have, though free from active malarial disease, chronically enlarged spleen; and we must also bear in mind that the possession of an enlarged spleen is no protection against other diseases, and that enlarged spleen is symptomatic of many diseases, febrile and other. I have several times seen ulcerative endocarditis in patients with spleens enlarged from antecedent malaria; a coincidence merely. The same occurrence I have often seen in phthisis, and in many septic conditions.

If quotidian fever associated with enlargement of the spleen is to be distrusted as a combination indicative of malaria, still more so is quotidian fever associated with enlargement of the liver. The latter combination usually means abscess of the liver. Any one who has had much experience of tropical practice must know that this disease is often, I might say generally, at all events in the earlier stages, diagnosed malarial fever. Osler says he has seldom seen an abscess of the liver in which the patient had not been liberally dosed with quinine. This is my experience likewise. I have seen a medical man make the mistake in his own person. The gentleman I refer to had been many years in India. He fell ill, and was invalided home. He had every afternoon a smart shivering fit, a rise of temperature to 103° or over, followed by drenching perspiration. He took large doses of quinine daily for many weeks. Finally, becoming very ill, he sent for me. I found the liver enlarged, tender, the spleen not enlarged, or only slightly; these facts, with the quotidian fever and other points, satisfied me that there was an abscess in the liver. But I could not convince the patient. He asked me to make a blood examination. I did so, after suspending the use of quinine for a week to give the hypothetical plasmodium a chance to get into the peripheral circulation. The result, so far as the presence of the parasite was concerned, was negative. Next, he insisted on another week of larger doses of quinine, and only then, and after much persuasion, did he accept my diagnosis and permit Mr. Godlee to open the large abscess in his liver. Fortunately he got well, but his conversion to the fallibility of quotidian periodicity as a diagnostic mark of malaria was somewhat dearly purchased.

Strange to say, syphilis, both secondary and tertiary, is not infrequently, on the strength of an associated quotidian fever and a residence or visit to a malarious country, diagnosed malaria. Some years ago I was consulted by a gentleman who had resided for many years in a mildly malarious country. The story he told me was that for over a year he had been suffering from ague. The attacks, he said, were quotidian and very severe. He had taken large doses of quinine and of arsenic, had visited hydropathic and similar health establishments, and done everything he could think of to get well. As soon as he told me the story of his treatment, for reasons which I will state by-and-by, I was quite sure he was not suffering from malaria, and proceeded to endeavour to ascertain

the cause and nature of his fever. In the course of my examination I found his liver very much enlarged, studded with irregular firm masses so big and hard that I thought they were probably malignant. I asked if any one had examined his liver before. He told me no one had done so recently; everyone had accepted his own diagnosis of his case (a very common practice, I am sorry to say), for, said he, of course he knew all about the symptoms of fever much better than any doctor, in this country at all events, could tell him. In going further into his history I ascertained that many years ago he had a chancre. In the hope, but I confess not with the expectation, that the lumps on his liver were syphilitic and his fever symptomatic of softening gummata, I put him on iodide of potassium. Two days later he called on me saying the medicine had given him headache and coryza, and so upset him that he had stopped taking it. After a good deal of trouble I persuaded him to double the dose. A week later he again called; this time with the news that his fever had vanished, his appetite had returned, and that he felt a new man. Gradually, under large doses of iodide, the irregularity and enlargement of the liver disappeared, and he got quite well.

Some time ago I saw in consultation a young gentleman who had been travelling in unhealthy countries, and who, soon after his return, had fallen sick with fever. He insisted to his medical attendant that it was a malarial fever contracted on his travels, and persisted in taking quinine. Not improving, and still believing that his fever was malarial, I was asked to see him. Beyond a quotidian fever there was no evidence of malaria about him; but we elicited a history of a sore on the penis some months before. Having been told by the doctor he saw then that the sore was a soft sore and of no importance, he had not thought it worth while mentioning this circumstance before. We changed the quinine for mercury, and in a very short time the fever vanished.

Septic absorption of pent-up pus is a well recognised cause of quotidian fever, not unfrequently attended with marked rigor and diaphoresis. Sometimes the most careful examination fails to determine the situation of the pus. Now, if suppuration of this description occurs in an individual who has resided in malarious countries the case is almost sure to be diagnosed malaria. I have seen many such cases. Some time ago I was asked to see a young gentleman who for a long series of weeks had been the subject

of a quotidian ague-like fever. He had travelled abroad. He had been seen by a number of eminent medical men, each of whom had given a different opinion, and prescribed an equal variety of treatment. I was asked to see the patient with the idea that the case might be malarial. I had no difficulty in pronouncing definitely against such a diagnosis, but what the nature of the case might be I did not pretend to know. Months later I met in the street a medical friend who devotes himself to throat and nose diseases. In the course of conversation he said, "By the way, you saw some time ago a Mr. So-and-so with Dr. ——?" "Yes," I said, "what about him? How is he? Is he dead yet?" "Far from that," my friend replied, "he is quite well. Some time after you saw him I was asked to examine his nose, which was bothering him, and by way of cleaning the passages preliminary to examination I syringed his nostrils with a warm alkaline solution. I did nothing more, and could see nothing wrong. But since that time he has had no recurrence of his ague-like attacks, and he is now quite well."

Some years ago I was asked to see a retired member of the Indian medical service, said to be suffering from malarial fever. I was told he had been treating himself, but had become alarmingly ill. On arriving at the house I found the patient insensible,—moribund, in fact. Another medical man had been called in by the wife, but neither he nor I for a time could get any light on the case. The wife could only tell us he had suffered much from fever both in India and since his return to England. We could find no evidence of enlargement of the spleen or other indication of visceral disease, such as might explain the situation. In looking round the room for bottles or other evidence of poisoning we came across a very ancient gum-elastic catheter. This gave the hint. On examining the patient's perinæum we discovered a huge abscess. This was freely incised—too late, unfortunately, to save the patient.

Pyelitis, catheter fever, pylephlebitis, empyema, phthisis, middle ear disease, elephantoid fever, the fever of early leprosy, the fever sometimes associated with gall-stones, these and many similar conditions occurring in patients from abroad, because they are accompanied by an ague-like quotidian fever, and because they occur in individuals who have been abroad, are constantly being diagnosed malaria, and treated as such. Therefore, I say, in approaching the diagnosis of a pyrexia in a possible malarial, while regarding tertian

and quartan periodicity as absolutely conclusive, attach no weight whatever to quotidian periodicity.

(2) *The Therapeutic Diagnosis.*—Whatever may be the case in certain malignant infections in tropical countries, quinine, properly given, so far as my experience goes, never fails to arrest a malarial attack occurring in this country, and this within 48, or at most 96, hours of its administration. Therefore, a periodic or remitting fever that persists after adequate dosing with quinine, say, for four days, is not malarial.

Everyone believes, or says he believes, in the anti-malarial virtues of quinine, but it is strange how little confidence some practitioners have in its diagnostic value. Thus I frequently see in consultation cases of fever, presumed to be malarial, which have been taking quinine in large doses for weeks, or even months, and yet no suspicion about the correctness of diagnosis had been entertained. When asked to see a case of supposed malarial fever of a persistent nature, my first question usually is, "Has the patient taken quinine, for how long, and in what doses?" If I am told, as is often the case, that he has had large doses for many days, I feel sure, without seeing the case, that it is not one of malaria. In this country, if any of you are called on to treat a fever you suppose to be malarial, and if this fever resist quinine properly given and in full doses for three or four days, my advice to you is to revise your diagnosis; the fever is not malarial. I could quote many cases in illustration. It is hardly necessary to do so. The case of liver abscess I have already related is a case in point.

There are two important matters, however, which require to be attended to in applying the quinine test:—First, the dose must be adequate; second, the quinine must be absorbed.

In many instances quite an insignificant dose will check an ague. Many years ago, while in practice in the island of Formosa, I ran short of quinine, and had to economise my very limited stock. With this object I experimented to ascertain the minimum dose that would check an ague, and ultimately came down to half a grain three times a day. My Chinese patients, in several instances, said they were cured by this insignificant amount—so potent is quinine in some cases of malaria. This winter I had in hospital a patient suffering from double benign tertian infection. By a properly timed small dose of quinine it is sometimes possible to eliminate, in such a case, one group of the parasites without injuring the other

group, and so to convert a quotidian ague into a tertian. I wished to demonstrate this to the students at the School of Tropical Medicine. I gave the patient three grains of quinine an hour, or thereabouts, before an expected paroxysm. Small though the dose was it killed out not only the group of parasites I proposed to eliminate, but the other group as well, and, contrary to my intention, cured for the time being the patient.

Quinine, as against the malaria parasite, is a very potent drug, but for reliable diagnostic, as well as for therapeutic, purposes it must be administered in much larger doses than those I have just mentioned. I would say that if a fever in this country resists 10 grains of quinine, given three times a day for four days, it is not malarial.

The dose of quinine should not only be adequate, but we must assure ourselves that it is absorbed. I am quite certain that many of the failures to control malaria by quinine are attributable to neglect of this essential. A catarrhal state of the gastric mucous membrane is usual in severe malarial attacks; such a condition is very unfavourable to absorption. Persistent vomiting is also common enough; food and drugs are alike rejected. To get the therapeutic action and diagnostic value of quinine in such circumstances the drug must be given hypodermically, or by enema.

Quinine nowadays is often given in tablet, or coated pill form; a most dangerous method in serious cases, and a most unsatisfactory one for diagnostic purposes. For some time quinine tablets have not possessed the flint-like hardness that used to characterise them a few years ago; they are now more soluble, but, even lately, twice I have seen them fail to be absorbed. In one case the patient developed a severe malarial attack on his way home from the Gold Coast. He took quinine tablets, and persisted in their use after his arrival in London. So much quinine did he take in this way without benefit, that both the patient and his medical attendant lost confidence in the drug, and the patient came very near dying. Three or four intramuscular injections of the acid hydrochloride broke the fever, and the patient quickly recovered.

In giving quinine, therefore, whether for therapeutic or for diagnostic purposes, we should assure ourselves that it is absorbed.

(3) *Microscopical Diagnosis.*—Of the three means for diagnosing malaria this is the most satisfactory, provided it is undertaken by one with large experience. A negative result by the amateur is

valueless; a positive result is not much more to be trusted. It takes a large amount of practice to be able to recognise all forms of the malaria parasite, or to discriminate between them and vacuoles in the red corpuscles in fresh films, or dirt in dried and stained films. Articles in the medical papers by amateurs in malarial blood examination sometimes supply amusing reading. The frequency with which such writers encounter malarial rosettes and flagellated bodies, and free flagella, forms of the parasite least frequently met with, is very suggestive. Free pigment—in reality dirt—they often see. White blood-corpuscles I have known described as malarial parasites; blood platelets, as spores or sporulating parasites; cotton fibres or fibrin, as flagella. No one without some knowledge of the histology of normal blood, and much experience of microscopical examination of malarial blood, should attempt to write on the subject of the malarial parasite, much less attempt responsible diagnosis of malaria with the microscope. The thing is easy enough when one has been properly taught, and after large experience. Then the microscope is invaluable in diagnosis; but those who have not been so taught, and who have not had much experience, are eminently unreliable—they are often worse than useless. Therefore, for the majority of medical men, if they wish to have blood examined for the purpose of diagnosis in regard to the presence of a possible malarial infection, the services of an expert are necessary. But, although he may not be able himself to diagnose malaria with the microscope, every medical man should know how to prepare blood films suitable for such an examination. Very singular notions are entertained about this. I have sometimes had blood sent me in capillary tubes, such as are used to hold vaccine. I have also had sent me blood so thickly smeared on a slide that the preparation would not transmit light. I have also had sent me, from a distance, an ordinary slip and cover-glass wet preparation, with a request to examine it for malaria. Blood transmitted in any of these ways is useless. Unless the fresh blood can be examined at the bedside, or within an hour or thereabouts of preparation, dried films should be made, and subsequently transmitted to the laboratory for fixing, staining, and microscopical examination.

There are many ways of preparing malarial blood films. I have tried most of them. The best, I believe, is that described by Drs. Christophers and Stephens, or some modification of this. An

ordinary microscope slip is carefully cleaned with alcohol. The patient's finger tip or the lobe of his ear is similarly cleansed. Finger or ear is then pricked with a clean and rather long ordinary sewing needle. A drop of blood is pressed out, and, as it may contain epithelial *débris*, wiped away. A second but very minute drop, the size of a large pin-head, is then expressed, and touched lightly (the skin must not be touched) with the clean surface of the slip about an inch from one end. Immediately the shaft of the needle is laid transversly on the droplet of blood so transferred to the slip. After waiting a second or two for the blood to run out by capillarity between the surface of the slip and the needle, the latter, held between finger and thumb, is drawn along the surface of the glass. In this way, with a very little practice, a beautifully fine and even film is produced. Half a dozen such films should be prepared. The single prick suffices, as the films can be made very rapidly one after another. After they have dried they should either be wrapped in very clean tissue-paper or placed in a dust-free slide-box, and transmitted to the laboratory. Here they are fixed with alcohol (five or ten minutes), and subsequently stained and examined.

For purposes of diagnosis I use either borax-methylene blue or dilute carbol thionine. These are very reliable stains, keep well, act rapidly, and give sufficiently good results. Undoubtedly one of the several modifications of Romanowsky's stain, when successful, gives a more brilliant picture; but they are somewhat unreliable, and unless the particular sample of stain employed is in frequent use, and known to be good, this method is not advisable for ordinary purposes of diagnosis. Leishman's modification of the Romanowsky method gives very beautiful results, and has the advantage of not requiring a preliminary fixation of the blood with alcohol, but it, too, has the objection of unreliability in ordinary clinical conditions. Malarial blood should not be fixed by heat.

In stained films, or in fresh blood, it is practically always possible to find the parasite—at all events in those cases of malarial infection that come to England. But this only on one condition, and this condition I would impress on you—the patient must not have taken quinine recently. You may find certain forms of the parasite —the crescent, for example—after full dosing with quinine, but the usual fever-causing forms, as a rule, rapidly disappear after

administration of the drug. Therefore if you wish to have a reliable microscopic diagnosis in supposed malarial fevers, do not give quinine, or suspend its use for some time, before preparing the blood slides.

It is difficult to over-state the value of the microscope in the diagnosis of malaria. I could quote many cases in illustration. I shall mention two only: one showing what may be gained by employing it; one showing what may be lost by not employing it.

Some months ago I was asked to see a patient in the Great Northern Hotel. I was told he had just returned from abroad and was very ill. He had been sent by Dr. A. Scott, of Brighton, who, suspecting malaria, advised, as the patient was passing through London *en route* for his home in the country, that I should be consulted. I found an emaciated, delicate-looking lad, with an appearance suggestive of phthisis. I tried to get from him his history and symptoms, but he would not converse. On being asked a question he would smile in a vacant sort of way, and perhaps, after a long pause, emit a monosyllabic answer, but it was impossible to extract any useful information from him. Manifestly he was off his head. His parents informed me that he was 20 years of age, and had been in a cattle and fruit ranche in Shaster County, California, since the spring of 1900. He got on well on the ranche, liked the life, and kept his health till July, 1901, when, judging from his letters home, he appears to have had a malarial attack. For some time after this the parents received no news of their son. Becoming anxious, they telegraphed on October 9th for information, and received for reply: "Son has changed for the worse, but doctor gives hope." Immediately on receipt of this alarming telegram they set out for California, and, on arriving at the ranche, found that their son had been sent on October 5th to the State Lunatic Asylum at Napa. Here they found him on October 30th in a deplorably dejected condition, emaciated, and so weak that they feared he would not stand the journey home. His disease was stated to be melancholia and mania. On the way home he was better and worse. Twice or three times on board ship he had feverish attacks, which came on about 10 p.m., and lasted till 2 a.m., and for which the ship's doctor gave him some small white tablets with an "A" stamped on them, doubtless antipyrin or antikamnia. This was the story I got on November 19th from his parents. On examination I found the patient free from fever; his

lungs were healthy, but his spleen was enlarged and slightly tender. I made films of his blood, which I examined the same afternoon. They showed many malarial crescents, and an abundance of the fever forms of the malignant tertian parasite. The patient was removed to St. George's Hospital and placed under Dr. Ewart. The same evening he had some fever, but full doses of quinine rapidly cleared his blood of the fever forms of the parasite. It was some weeks, however, before the crescents entirely disappeared. Under quinine the mental and physical condition gradually improved. There was no more fever, and he was discharged a month later free from malarial symptoms, but still somewhat slow in answering questions, and still mentally debilitated. I have little doubt that had the microscope been used earlier the true nature of this painful case would have been ascertained and suitable treatment instituted. Though employed dangerously late, I believe the microscope saved this lad's life, and perhaps his reason.

An officer of a liner trading to the East was brought on a stretcher to the Seamen's Hospital, Albert Docks, on July 30th, 1901. The history received with the patient was that his ship had just returned from the Mediterranean, where it had been running between Brindisi and Port Said, and that he himself had been in perfect health till three days before admission. He had never suffered from malaria. About that time he was walking about; but, looking ill, he was sent to his bed by the ship's surgeon. Presently he vomited blood, and passed large quantities of blood by stool, and, continuing to do so, was taken to hospital. On admission he was collapsed, with a temperature of 102·8°. Towards evening the temperature fell to 98·4°; hæmatemesis and melæna persisted. He had much abdominal pain, temperature fell to 96·4, the pulse became rapid, and he died next day. At the *post-mortem* examination the spleen was found slightly enlarged; the pancreas intensely congested and containing minute extravasations of blood; the mucous membrane of the stomach and upper part of the small intestine was similarly congested and studded over with ecchymoses. At the time the case was supposed to be one of hæmorrhagic pancreatitis. Pieces of the pancreas and intestine were preserved for microscopical examination. Owing to press of tutorial work at the School of Tropical Medicine, Dr. Daniels was unable to examine or make microscopical sections of the organs.

But when, at the conclusion of the session, he had leisure to do so, he was astonished to find that the capillaries of the pancreas and intestinal mucosa were packed with sporulating malignant tertian parasites. Drs. Ross and Daniels have recorded and illustrated this very interesting case in the 'Journal of Tropical Medicine,' February 15th, 1902. None of us suspected malaria. The patient had not resided in any malarial place. There can be little doubt, however, that while his ship lay alongside the wharf at Brindisi, or, perhaps, during a short run on shore, this gentleman was bitten by infected anopheles, and thus received his fatal illness. Had his blood been examined earlier in the disease, or even within an hour or thereby of his admission into hospital, the true nature of the case could have been recognised, and the patient's life, perhaps, saved by timely hypodermic injections of quinine.

In rare instances, and at certain times in a considerable proportion of cases, the parasite, or its product melanin, even in severe infections, may not be detectable in the peripheral blood, and, as I have mentioned, even small doses of quinine, though therapeutically insufficient, may cause its disappearance temporarily, or, in the case of cure, for good. Even in these circumstances it would seem that the microscope may be relied on for a diagnosis.

It has been known for some years that during, and for some time after, malarial attacks the leucocytes are greatly diminished in proportion to the red blood-corpuscles. The diminution, however, is principally in the polymorphonuclears and lymphocytes, so that there is a relative increase in the large mononuclears. Drs. Christophers and Stephens, fixing their attention on this point, have marked out a method by which it is possible to give a fairly reliable diagnosis of actual or recent malarial infection, and this no matter whether quinine has been administered or not. The increase in the mononuclears, they state, is principally during the apyretic intervals, setting in as soon as the temperature begins to fall. They say, in a report to the Royal Society, that "an increase beyond 15 per cent. is proof of an actual or recent malarial infection."

Captain Leonard Rogers, I.M.S., after a very careful investigation of the point, endorses ('Brit. Med. Journ.,' April 5th, 1902) this opinion. He concludes: "An increase in the large mononuclears to about 12 per cent. and upwards, especially during the remissions of the temperature, strongly indicates malaria."

Dr. Daniels, Superintendent of the London School of Tropical Medicine, has paid a great deal of attention to this point. In reply to a request for a statement of his views, he writes :—

"*Leucocytic Variation after Malaria.*—In all forms of malaria after, and to a smaller extent during, the fever, the large mononuclear leucocytes are relatively increased to the other leucocytes.

"This increase may be slight, and in certain cases has been so slight that they only formed 15 per cent. of the leucocytes. Commonly after malaria they vary from 25 to 30 per cent., and occasionally are over 40 per cent.

"The increase does not seem to be dependent on the species of parasite, on the number of parasites present during the acute attack, or on the severity of the symptoms or sequelæ. It is maintained for a period varying in different cases from two or three weeks to at least as many months, and slowly diminishes.

"It is not affected by quinine, either in large or frequently repeated doses.

"With some exceptions it affords a satisfactory proof of the probable recent presence of parasites.

"In normal blood it is rare to find more than 12 per cent., though I have seen as high a percentage as 16. In typhoid and Malta fever I have seen a similar increase, but it is exceptional. It is said to occur in small-pox. In certain diseases, particularly scurvy, there is also a marked increase; but in this disease there is also leucocytosis, and a more marked increase in the lymphocytes.

"The absence of this variation is of more value as a diagnostic point than its presence. As far as I have worked with the method, the only exceptions I have seen were when an intercurrent disease, such as pneumonia, which is associated with increase in the polymorphonuclear elements, also occurs. In other cases it has shown itself to be a reliable method for the exclusion of recent malaria.

"Working for three sessions with classes of students of 20 odd, many of whom, coming from the tropics, have suffered from malaria, this test has readily discriminated those of the students who have recently had malaria from those who have not.

"It has proved of value in differentiating cases of yellow fever from malaria (Low and Gray in St. Lucia).

"It has proved of value in differentiating hyperpyrexial fever of West Africa from malaria (Sims, Congo).

"Though not of the same value as the presence of parasites, or of pigmented leucocytes, or recent pigment in the organs, it is of much higher value as a test of recent malaria than splenic tenderness or enlargement, and is of particular importance in cases where, either in the natural course of events, or after the administration of quinine, there are no characteristic symptoms.

"It is probably of about the same value as the agglutination test in typhoid, with moderate dilutions of the serum—say, 1 in 20.

"The main objection to the method is the difficulty that is sometimes present in deciding which are large mononuclears and which are lymphocytes. After actual practice this difficulty is small, and a column for undecided or doubtful leucocytes will be found useful at first. After a short time this will be, in the majority of cases, little used. In these determinations, however, there is a certain personal equation, so that counts made by different individuals vary within small limits."

These are Dr. Daniels' opinions, and, being based on large experience, I attach much value to them.

A few weeks ago I saw in consultation a gentleman recently returned from abroad. On the previous Saturday he was suddenly seized with a rigor and fever; on the Sunday he had no fever; on the Monday he had another paroxysm, and his temperature kept a degree or two above normal during Tuesday. I saw him on Wednesday morning. His temperature was then normal. He had received a few small doses of quinine. The tertian periodicity of the fever and a slightly enlarged spleen indicated a malarial attack, but to make certain I examined a film of his blood. As might have been expected from the quinine he had taken, there were no parasites, but a count of the leucocytes gave 20 per cent. large mononuclears, thereby confirming the clinical diagnosis. It is under such circumstances that a study of the leucocytic counts and variation will be of service in helping to correct diagnosis, and also in discriminating malaria from such conditions, as abscess of the liver, pneumonia and so forth, in which there is a leucocytosis; from typhoid, in which the lymphocytes are increased; and from other diseases with similar characteristic blood changes.

It is difficult to overrate the practical value of blood examinations. Only last week I had a striking illustration of this. A lady from India consulted me about what she described as an enlarged

spleen. She had lived in a malarious district, and in years gone by had suffered a great deal from malarial fever; less so of late years. Medical men in India had told her she was "saturated with malaria." She came home on account of her health, especially on account of the enlarged spleen. She was rather emaciated, anæmic, and sallow. On examining the abdomen I found the pelvis and right side of the abdomen filled with a large, somewhat movable, rounded tumour. There was a notch low down on the right margin of the tumour, but there was an equally pronounced notch, if not two notches, on the left border. The tumour was not connected with the liver, and the whole of the *left* hypochondrium was resonant and soft. No indication of a spleen could be detected in the usual situation of that organ. The patient was positive, however, that the tumour began in the left hypochondrium, and that it was only recently that this part had become soft. Feeling puzzled about the case, I sent the patient to Mr. Meredith for examination of the pelvic organs, and, if thought desirable, for exploration or operation. Mr. Meredith was equally puzzled. The uterus and ovaries were not involved. We advised the patient to go to a nursing home with a view to exploration. At our first interview I had made some films of her finger blood, but being busy did not overtake their examination till two days later. You may judge of my astonishment, and of my thankfulness that our operative suggestions had not gone further, when, instead of finding a slight increase of large mononuclear white blood-corpuscles, indicating recent malarial infection, I found that our patient was suffering from advanced spleno-medullary leucocythæmia. The tumour we were puzzled about was undoubtedly an enlarged leucocythæmic spleen, which had, in consequence of its weight and size, become displaced.

We sometimes get assistance in concluding for or against malaria from considerations of time and locality. It is very commonly believed that a malarial infection may last a lifetime. Thus the old Indian, many years after he has come home for good, may tell us that he has recurrences now and again of a jungle (that is, malarial) fever contracted in youth. I do not believe in the malarial nature of such attacks. I have never been able to find the parasite in any such case. My belief is that malarial infection does not persist after three years from the date of invasion. Of course a patient can become re-infected—that is another affair; but I do not think

the duration of any given infection exceeds three years. I will not be positive about this; we want more observations. But in my experience a malignant tertian tends to die out in from 18 months to two years, a benign tertian in about two to two and a-half years, a quartan in about three years. We know that other protozoal organisms having asexual and sexual phases require resuscitation by passing through the sexual phase every now and again; otherwise they become extinct. I believe the same to be the case with the malarial parasite. Other people besides the old Indian get feverish colds and different kinds of short febrile seizure, but because they have never been in India or Africa they call them influenza or what not. Had the old Indian never been to India he would do the same. He is rather proud of his jungle fever, and sticks to it longer than it sticks to him. While alive to the possibility of my being wrong in my belief, I am inclined to regard any fever which occurs three or more years after the patient has been away from the possibility of fresh malarial infection as non-malarial.

If a patient has never been to a malarial country he cannot get malaria, unless by artificial or abnormal means. In the malarial belt there are many non-malarial places—Malta, for example. A chronic or recurring fever from Malta in a person who has not visited a malarial place is probably Malta fever or enteric, certainly not malaria. Similarly, Barbados is not malarial. Therefore a chronic or recurring fever in a patient from Barbados who has never visited a malarial place cannot be malarial; most probably it is the fever symptomatic of some of the lesions in filariasis so common in Barbados. Commonly enough, because such fevers are ushered in by severe rigor, these filarial fevers are locally known as "ague." This is a misnomer, they have nothing to do with malaria.

I have seen a good many reputedly malarial patients from the Fen districts and other formerly malarious spots in England. On critical examination not one of them has turned out to be malarial. They were assumed to be malarial because there was some periodicity about the fever, perhaps enlarged spleen, and because they came from localities which were formerly malarious. I have never seen a case of indigenous English malaria. I believe the plasmodium has died out in England, like the wolf and the wild boar.

In concluding these rambling and disconnected, but I trust practical remarks, I would again impress on you the importance

of a thorough reliance on the three classical methods of diagnosing malaria:—The clinical—tertian and quartan periodicity; the therapeutic—the curative effect of quinine; and the microscopical—the detection of the parasite or its products in the blood, and the characteristic leucocytic variation. A thorough and intelligent application of one or all of these methods seldom, if ever, fails to lead to a correct diagnosis for or against malaria. At the same time I would warn you that although a positive diagnosis of malaria may be indicated in some given case, the presence of malaria does not exclude other diseases. On the contrary, malaria often predisposes to other infections. Similarly, the explosion of a latent malaria is favoured by other infections, especially typhoid and tuberculosis.

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